DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/07 has been entered. Claims 63, 64, 66, and 68-74 were pending. Applicants added claims 75-77 and amended claims 63, 66, 72, and 74. Therefore, claims 63, 64, 66, and 68-77 are currently pending. Claims 64 and 68-70 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 63, 66, and 71-77 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 1290 and/or 119(e) as follows:

This application is a CON of 09/526,106 03/15/2000 ('106), which claims benefit of 60/175,968 filed 01/13/2000 ('968) and claims benefit of 60/135,926 filed on 05/25/1999 ('926)

and claims benefit of 60/124,339 filed on 03/15/1999 ('339). However, one or more of the applications stated above fail to provide adequate support under 35 U.S.C. § 112, first paragraph for the claimed invention as follows:

> (A) For ***claims 63, 66, and 71-77***, none of the applications provide support for the current genus of fragment complementation systems wherein "said first and second break-point termini are between 2 amino acid residues in a solvent exposed loop between amino acid residues Thr 195 and Ala 202 " (e.g., see New Matter Rejection below).
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> (B) For ***claims 72-77***, the '339 application fails to provide support for peptides segments that "enhance" functional reconstitution including HSE, EKR, QGN, DGR, GRR, and GNS.
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> (C) For ***claims 72-77***, the '926 application fails to provide support for peptides segments that "enhance" functional reconstitution including HSE, EKR, QGN, DGR, GRR, and GNS.

If applicant believes this assessment is in error, applicant must disclose where in the specification support for these limitations can be found. See MPEP § 714.02. Therefore the filing date of the instant application is deemed to be its actual filing date, **September 22, 2003**.

3. Applicant states that this application is a continuation or divisional application of the prior-filed application (see above). A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the following matter not disclosed in the prior-filed application: See New Matter rejection below.

Response

4. Applicant's arguments directed to the above denial of 35 U.S.C. §§ 119(e) and120 priority were considered but deemed non-persuasive for the reasons set forth below.

[1] Applicants argue, "claim 63 as amended has specific expressed support in the instant application as filed, the '106 parent … and in '339" (e.g., see 10/29/07 Response, pages 11 and 12, especially paragraph bridging pages 11 and 12).

[1] The Examiner respectfully disagrees for the reasons set forth in the New Matter rejection below.

[2] Applicants argue, "With regard to … the specific tri-peptides that enhance functional reconstitution … Applicants note that [these peptides] are supported in the '106 application at example 6 … Moreover, this same table listing … can also be found at page 17 of … '968" (e.g., see 10/29/07 response, page 12).

[2] Applications '106 and '968 are not in dispute. Consequently, Applicants' arguments are moot (e.g., see above wherein the '926 and '339 applications are called into question).

Withdrawn Objections/Rejections

5. The 35 U.S.C. § 112, first paragraph rejection denoted "A" is view of Applicants' amendments to claim 63. The 35 U.S.C. § 112, second paragraph rejection denoted "A" is withdrawn in view of Applicants' arguments (e.g., see 10/29/07 response, page 14, section VIII). All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. § 102

6. Claims 63, 66, 71 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Wehrman et al. (Wehrman et al. "Protein-protein interactions monitored in mammalian cells via complementation of β-lactamase enzyme fragments" *PNAS* **March 19, 2002**, *99(6)*, 3469-3474) (3/18/04 IDS, AB).

For ***claim 63***, Wehrman et al. disclose a fragment complementation system (e.g., see Wehrman et al., title wherein a β-lactamase complementation system is disclosed). In addition, Wehrman et al. disclose a first oligopeptide sequence and a second oligopeptide sequence wherein said first oligopeptide sequence is a fusion protein comprised of, in the direction of translation, an N-terminal fragment of a Class A β-lactamase protein no less than 25 amino acids in length fused through a first break point terminus to a first flexible polypeptide linker and a first interactor domain (e.g., see figure 1A; see also page 3470, column 2, second to last paragraph wherein the "197 β-lactamase fragment was fused to the amino terminus of the Fos helix [i.e., an interactor domain]"; see also figure 1 showing use of $(Gly_4Ser)_3$ linkers). Wehrman et al. also disclose a said second oligopeptide sequence that is a fusion protein comprised of, in the direction of translation, a second interactor domain and a second flexible polypeptide linker fused through a second break point terminus to a C terminal fragment of a class A β-lactamase protein not less than 25 amino acids in length (e.g., see figure 1A; see also page 3470, column 2, second to last paragraph wherein the "198 fragment fused to the carboxyl terminus of the Jun helix [i.e., an interactor domain]"; see also figure 1 showing use of $(Gly_4Ser)_3$

linkers). In addition, Wehrman et al. disclose wherein said first and second break-point termini are between 2 amino acids residues in a solvent exposed loop between amino acid residues Thr 195 and Ala 202 (e.g., see figure 1 wherein 197/198 junction is disclosed). Finally, Wehrman et al. disclose wherein upon binding of said first interactor domain with said second interactor domain said N-terminal fragment and said C-terminal fragment reconstitute to form a functional class A β-lactamase protein (e.g., see abstract; see also Results section; see also figures 2-4).

For ***claim 66***, Wehrman et al. disclose fragment complementation wherein said Class A β-lactamase protein comprises SEQ ID NO 2 with the E197/L198 junction (e.g., see figure 1).

For ***claim 71***, Wehrman et al. disclose the fragment complementation system of claim 63, wherein said first polypeptide linker is 3-30 amino acids in length; and wherein said second polypeptide linker is 3-30 amino acids in length (e.g., see figure 1; see also page 3470, column 2, second to last paragraph wherein the $(Gly_4Ser)_3$ linker is disclosed for each).

For ***claim 72***, Wehrman et al. disclose the fragment complementation system of 71 further comprising a first complementation enhancement peptide fused between the N-terminal fragment of the Class A β-lactamase protein and the first polypeptide linker and a second complementation enhancement peptide fused between the C-terminal fragment of the Class A β-lactamase protein and the second polypeptide linker (e.g., see page 3471, column 1, paragraph 1; see also page 3470, column 2, last two paragraphs wherein HSE,

GRE, EKR, and NGR are disclosed).

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the reasons set forth below.

Applicants argue, "The claims as presently amended are supported by at least the ('106 app.) as indicated above … [Therefore,] Wehrman et al. is not prior art … ." (e.g., see 10/29/07 Response, pages 13 and 14, especially page 14, paragraph 1).

Applicants have not been afforded priority as discussed above and, as a result, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. § 102/103

8. Claims 63, 66, and 71 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, 35 U.S.C. § 103(a) as being unpatentable over Michnick et al. (U.S. Patent No. 6,828,099) (Filed May 31, 2001) alone or in view of Galarneau et al. (Galarneau et al., "β-Lactamase protein fragment complementation assays as *in vivo* and *in vitro* sensors of protein-protein interactions" *Nature Biotechnology* **2002**, *20*, 619-622) as further evidenced if necessary by Applicants' Exhibit 1 filed 10/25/06.

For ***claim 63***, Michnick et al. (see entire document) disclose a fragment

complementation system (e.g., see Michnick et al., abstract), which anticipates the claimed invention. For example, Michnick et al. disclose a first oligopeptide sequence and a second oligopeptide sequence wherein said first oligopeptide sequence is a fusion protein comprised of, in the direction of translation, an N terminal fragment of a Class A β-lactamase protein no less than 25 amino acids in length fused through a first break point terminus to a first flexible polypeptide linker and a first interactor domain (e.g., see Example 2 wherein FRB-5a.a.-BLF[1] is disclosed, in this scenario FRB = interactor domain and BLF[1] = 23-197 of TEM-1 β-lactamase fragment and the 5 amino acids represents the linker). In addition, Michnick et al. disclose a second oligopeptide sequence that is a fusion protein comprised of, in the direction of translation, a second interactor domain and a second flexible polypeptide linker fused through a second break point terminus to a C-terminal fragment of a class A β-lactamase protein no less than 25 amino acids in length (e.g., see Example 2 wherein FKBP-5a.a.-BLF[2] is disclosed, in this scenario FKBP is the interactor domain and BLF[2] = 198-286 of TEM-1 β-lactamase fragment and the 5 a.a. represents the linker). Michnick et al. do not explicitly disclose the limitation "in the direction of translation" for either fragment, however, both the orientation disclosed in Michnick et al. and the opposite orientation as disclosed by Galarneau et al. (e.g., see figure 2 of Galarneau et al. wherein a 15 amino acid linker was used to connect to two fragments with the claimed orientation instead of two interactor domains) would be immediately envisioned because these are the "only two" orientations that preserve protein folding as exemplified, for example, by Applicants' exhibit 1

(submitted 10/25/06). That is, protein folding is only preserved when a linker or pair of interactor domains bind to the same side of the protein (i.e. see exhibit 1, top figure), not to opposite ends (i.e., see exhibit 1, bottom figure). Therefore, a person of skill in the art would immediately envision both the "insert" and "circular permutation" orientations. *In re Petering* 133 USPQ 275 (CCPA 1962); see also *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); see also MPEP § 2131. Alternatively, Michnick et al. inherently disclose this feature in accordance with *In re Graves*, 69 F.3d 1147, 36 USPQ2d 1697 (Fed. Cir. 1995) (prior art reference disclosing a system for testing the integrity of electrical interconnections that did not specifically disclose simultaneous monitoring of output points still anticipated claimed invention if simultaneous monitoring is within the knowledge of a skilled artisan). Here, fusions in the claimed orientation are shown to be within the knowledge of a skilled artisan by Galarneau et al. (e.g., see Galarneau et al., figure 2) showing the proper orientation in the QI construct using linker instead of a pair of interactor domains. In addition, Michnick et al. disclose wherein said first and second break-point are between 2 amino acid residues in a solvent exposed loop between amino acid residues Thr 195 and Ala 202 (e.g., see Example 2 wherein the break-point is at positions 197/198, see also column 2, lines 17-33 indicating that positions 196-200 form a solvent exposed loop; see also figure 1). Finally, Michnick et al. disclose binding of said first interactor domain with said second interactor domain said N terminal fragment and said C-terminal fragment reconstitute to form a functional class A β-lactamase protein (e.g., see figure 4; see also column 3, first full paragraph; see also column 5, lines

43-54).

For ***claim 66***, Michnick et al. also disclose a Class A β-lactamase protein comprises SEQ ID NO 2 (e.g., see Example 2; see also column 1, line 33 disclosing accession number AAB59737). Michnick et al. also disclose said first β-lactamase protein break-point and said second B-lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues in SEQ ID NO 2 selected from the group consisting of P149 and N150 El72 and L173 K190 and V191 A202 and G203 and G228 and K229 (e.g., see Example 2 wherein the 197/198 break-point is dislosed that is within 10 amino acids of K190/V191 or A202/G203).

For ***claim 71***, Michnick et al. also disclose a fragment complementation wherein said first oligopeptide further comprises a first polypeptide linker that separates the N-terminal fragment of a Class A β-lactamase protein from the first interactor domain wherein said first polypeptide linker is 3-30 amino acids in length and said second oligopeptide further comprises a second polypeptide linker that separates the C-terminal fragment of a Class A β-lactamase protein from the second interactor domain wherein said second polypeptide linker is 3-30 amino acids in length (e.g., see Example 2 disclosing the 5 amino acid linker Gly-Gly-Gly-Gly-Ser in each case).

In the alternative that the prior art teachings of Michnick et al. differ from the claimed invention, the difference is set forth as follows:

For ***claim 63***, Michnick et al. fail to teach the a β-lactamase protein covalently bonded "through the C-terminus" of a first class A β-lactamase protein break-point to a

first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A β-lactamase protein covalently bonded "through the N-terminus" of a second class A β-lactamase protein break-point to a second interactor domain (i.e., this corresponds to the "insert" orientation disclosed in figure 2 of Galarneau et al. wherein a 15 amino acid linker was used to connect to two fragments with the claimed orientation instead of two interactor domains). To the contrary, Michnick et al. disclose just the opposite orientation (i.e., the "circular permutation" orientation, see Galarneau et al., figure 2) wherein a β-lactamase protein is covalently bonded "through the N-terminus" away from the first class A β-lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A β-lactamase protein is covalently bonded "through the C-terminus" of a second class A β-lactamase protein away from break-point to a second interactor domain.

However, Galarneau et al. teach the following limitations that are deficient in Michnick et al.:

For ***claim 63***, Galarneau et al. (see entire document) teach the use of rejoining the fragments (albeit with a linker instead of a pair of interactor domains) using the currently claimed orientation (e.g., see figure 2 wherein the QI construct possesses a linker that joins the BLF[1] fragment to he BLF[2] fragment at the 196/198 junction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to join the interactor domains to the BLF[1] and BLF[2] fragments using their C- and N-termini, respectively (referred to as the "insert"

orientation), because Galarneau et al. show that this orientation will not destroy the proper folding and hence activity of the enzyme (e.g., see figure 2, QI construct). Furthermore, a person of ordinary skill in the art would have been motivated to use this orientation instead of the reverse N- and C- termini for BLF[1] and BLF[2], respectively (referred to as the "circular permutation" orientation), because Galarneau et al. disclose that the "insert" orientation retains approximately 40% of the enzymes wild type activity whereas the "circular permutation" orientation retains only about 20% of the enzymes wild type activity (i.e., the "insert" activity is twice as good). Finally, a person of skill in the art would reasonably have expected to be successful because the "insert" orientation does not destroy the proper folding of the enzyme by "reversing" on of the subunits.

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 102/103 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the reasons set forth below.

Applicants argue, "As indicated above, the claims as presently recited are supported by the priority documents … Therefore, the cited references are not prior art … ." (e.g., see 10/29/07 Response, page 14, section VII).

The Examiner respectfully disagrees. As noted above, the priority documents do not provide the requisite support for the current claims and, as a result, Applicants' arguments are

moot.

Accordingly, the 35 U.S.C. § 102/103 rejection cited above is hereby maintained.

New Rejections/Objections

Objections to the Claims

10. Claim 63 is objected to because of the following informalities:

A. Claim 63 is missing a comma after "fusion protein comprises of" in line 3. Correction is respectfully requested. That is, lines 3 and 4 should read, "wherein said first oligopeptide sequence is a fusion protein comprises of, in the direction of translation, an N-terminal fragment … ." Likewise, a comma is missing for the "second" fusion discussed in lines 7 and 8.

Claims Rejections - 35 U.S.C. § 112, first paragraph

11. Claims 63, 66 and 71-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

AA. Claim 63 was amended in the 10/29/07 response. However, the Examiner cannot find support for this amendment. Specifically, the specification does not provide support for "wherein said first and second break-point termini are between 2 amino acid residues

in a solvent exposed loop between amino acid residues Thr 195 and Ala 202" that "reconstitute to form a functional Class A β-lactamase protein." To the contrary, the specification reads, "An exposed loop was identified by this method between two α-helixes of E. coli TEM-1 β-lactamase (approximately Thr195 to Ala 202, between helixes 7 and 8) within which the chain could be broken to produce fragments which could only complement for activity [i.e., reconstitute to form a functional lactamase] when fused to the fos and jun helixes." Thus, Applicants make clear in their specification that a functional enzyme for this loop will only result when fos/jun is used. Other heterologous domains were disclosed in the following sentence including scfv, etc. but this applied only to the contiguous 197/198 junction, not the entire 195-202 loop. In addition, only TEM-1 β-lactamase of *E.coli* was used, not the currently claimed genus of Class A β-lactamases from any source. For example, Wikipedia indicates that approximately 140 TEM-type "class A" enzymes are known including TEM-10, TEM-12, and TEM-26 (e.g., Wikipedia, the Free Encyclopedia. Beta-lactamase. Retrieved at http://en.wikipedia.org/wiki/Beta-lactamase on June 8, 2008, pages 1-11). In addition, "Class A" enzymes exhibiting far less homology such as SHV-1 (~68% homology) and CTX-M (~40% homology) are also known (e.g., see Wikipedia, page 5, SHV and XTX-M sections). Applicants' specification and priority documents do not describe SHV and CTX-M "class A" β-lactamases. In addition, Applicants fail to describe any other members of the TEM class (e.g., TEM-10, TEM-12, etc.) other than TEM-1. That is, Applicants only conducted a search of the "fragment space" for TEM-1 β-lactamse, not

"any" class A enzyme. Further, Applicants admit that a thorough search of the fragment space is required to determine which fragments will reconstitute to form an active enzyme and cannot be determined by looking at the three dimensional structure of the molecule (e.g., see '926 priority document, page 4, last full paragraph, "However, the best fragments for such assisted complementation can not be found by examination of static 3-dimensional structures, but rather can only be found by conducting a thorough search of the 'fragment space' of the enzyme in question for fragments which perform in the desired manner under the desired conditions."). Further, Applicants' cited passages in the current application and priority documents (e.g., see 10/29/07 response, pages 9-11) fail to refute this position.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639